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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,299	BARSOUM ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 34-54* is/are pending in the application.

4a) Of the above claim(s) *50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,34-49 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to restriction requirement of 5/16/05 has been entered.

Claims 1 and 34-53 are presently pending.

Applicant's arguments vis-a-vis the preliminary amendment being filed before the present amendment practice took effect are noted (Applicant's response of 5/16/05, pp. 9-10), but are moot, because the Examiner did enter the amendment (Official Action of 4/14/05, p. 2, paragraph 3).

It is noted that, due to typographical error, the Examiner did not include claim 54 in the restriction requirement of 4/14/05, and that such claim was meant to be included in Group I of the restriction requirement. However, because Applicant makes the same argument for inclusion of such claim in Group I, in the response to restriction requirement of 5/16/05, p. 9, the claim 54 will be considered to have been included in Group I.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Election/Restrictions

Restriction of Invention

With regard to the restriction requirement, Applicant's election of Group I, claims 1, 34-49, and 52-54, in the reply filed on 5/16/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 50-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/14/05.

Election of Species

Applicant's elections of the species of "human" and "intravenous administration", and related arguments are noted, and the Examiner therefore withdraws the species election requirements.

Conclusion to Restriction/Election

For the reasons given above, claims 1, 34-59, and 52-53 are presently considered with respect to the elected species "human".

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the brief description of the drawings contains references to Figures 6a-6e, and the drawings contain five graphs on the page indicated Figure 6; however, which figure is 6a, 6b, 6c, 6d, and 6e is not clear. Applicant is required to label the figures properly. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 is rejected because while claiming a method of modulating toxicity associated with a virally encoded transgene, only requires the administration of an agent, and does not require the administration of any virally-encoded transgene. Hence, it is unclear how the method is effected: i.e., there is no nexus between the claimed method and the steps of the method.

Claim 48 is rejected because while requiring that the agent of claim 47 to be administered before administration of a therapeutic nucleic acid encoding a therapeutic transgene, claim 47 does not require transgene, and the method does not "further comprise" administration of such nucleic acid.

Claim Rejections - 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-37, 39, 41-42, 44-49, and 52-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34-37, 39, 41-42, 44-49, and 52-53 encompass any agent that modulates Kupffer cell function and/or any modulation of Kupffer cells.

The specification describes that prior administration of agents that decrease the number of Kupffer cells increases the subsequent levels of transformation, and heterologous transgene expression, from adenovirus-encoded transgenes, which are subsequently administered (SPECIFICATION, p. 3, paragraph 2; pp. 14-15, paragraph bridging). Moreover, such agents that decrease Kupffer cell levels and provide for subsequent higher transgene expression from adenovirus transformations, subsequently administered (e.g., Wolff, et al. (1997) J. Virology, 71(1) 624-29). Further, with regard to agents that modulate Kupffer cell function and any modulation of Kupffer cells, the specification states:

> While not wishing to be bound by theory, it is believed that delivery of low doses of adenoviruses in a subject results in preferential uptake of the adenoviruses by the subject's Kupffer cells. The Kupffer cells sequester the low doses of viruses without expressing the transgene and present a blockade to viral transduction. Once this blockade is saturated, efficient gene delivery of a virally-encoded therapeutic gene product (such as IFN-[beta]) to the subject can be achieved. Therefore, a therapeutic nucleic acid provided in, *e.g.*, a viral vector, such as an adenovirus vector, can be efficiently delivered to the subject if administered with an agent that saturates the viral uptake capacity of Kupffer cells, or by lowering levels of Kupffer cells. In one embodiment, the delivery is intravenous delivery. In addition, the subject comprises cells capable of expressing the transgene.

SPECIFICATION, pp. 2-3, paragraph bridging.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to

show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant, and the art, provide a wide variety of agents that decrease the levels of Kupffer cells (e.g., Wolff, (ABOVE); SPECIFICATION, pp. 14-15, paragraph bridging). Moreover, Applicant supplies a single agent that modulates some aspect of Kupffer cells, allowing subsequently administered adenovirally-encoded transgene expression to be increased, which agent is an adenovirus (SPECIFICATION, p. 2, paragraph 2; EXAMPLES). However, even Applicant admits that they do not know how the adenovirus works, and which aspects of Kupffer cell function are effected, to allow subsequent increases in transformation of non-Kupffer liver cells (See quotation, ABOVE). Moreover, the specification does not provide any disclosure as to what would have been the required structure which would cause any modulation of Kupffer cells or Kupffer cell function. Furthermore, such modulation of Kupffer cells or Kupffer cells is not supported by logic. To wit, an agent that increases the proliferation

of Kupffer cells and an agent that increases Kupffer cell activity, which would both be encompassed by "modulation", would necessarily equate with increased depletion of subsequently administered adenovirus. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are the functional characteristics discussed above.

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any agent that modulates Kupffer cell function or any modulation of Kupffer cells, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 38-46, and 52-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) a method for increasing the level of a therapeutic gene product in the liver of a subject, the method comprising administering to said subject a first adenoviral vector comprising a heterologous transgene encoding said therapeutic transgene product, operably linked to expression control elements for expression in hepatocytes and a second adenoviral vector that does not comprise said transgene, wherein said second adenoviral vector is administered prior to, or concurrently with, said first adenoviral vector, wherein each vector is administered intravenously, intraperitoneally, or directly to the liver; and

(ii) a pharmaceutical composition comprising an adenovirus encoding a therapeutic gene product encoding a therapeutic transgene operably linked to expression control elements for expression in liver cells, a second adenovirus not encoding such transgene, and a pharmaceutically-acceptable carrier,

does not reasonably provide enablement for increasing gene product levels in any tissue other than liver, any viral vector for modulating Kupffer cell function, any viral vector for transforming liver cells, any method of administration, any transgenes not operably linked to expression control elements for expression in liver cells, administration of the adenoviral vector not encoding the transgene subsequent to the administration of the adenoviral vector encoding the transgene, administration of any viral nucleic acid, the transformation of any tissue, or particles outside the range of 70-100nm that modulate Kupffer cell function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Note, RE Claim Interpretation

As a preliminary note, it is noted that Applicant's claims encompass agents that modulate Kupffer cell function (e.g., claims 1, 34, 36, 37, and 52), as well as agents that modulate Kupffer cell function or modulate Kupffer cell level (e.g., claim 47). The Examiner asserts that the reasonable interpretation of the separation of these limitations in, e.g., claim 47, to mean that modulation of Kupffer cell function is separate and distinct from that of modulation of Kupffer cell level. Hence, as will be shown below, not only is claim 47 not enabled, but the other independent claims are limited in scope to agents that modulate Kupffer cell function, which agents are adenoviruses, and further, due to the size of such particles, are limited to 70-100nm in size.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue

experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its fully-claimed scope, and that, therefore, Applicant's claims are not enabled for their fully-claimed scope.

The Breadth of the Claims

Claims 1, 38, 40, 43, and 54 encompass a method for increasing the level of a therapeutic gene product in any tissue(s) of any subject, comprising administering, via any method(s), any first viral vector comprising a nucleic acid encoding the gene product, and any viral vector that does not comprise the transgene and modulates Kupffer cell function in the subject, and such vectors may be concurrently, or one after the other, with no order in time or method of

administration. The dependent claims limit at least one vector to being an adenovirus or being replication defective, the subject to any rodent, or 15 different methods of administration.

Claims 34-35 encompass a method for increasing the level of a therapeutic gene product in any tissue(s) of any subject, comprising administering, via any method(s), any viral vector comprising a nucleic acid encoding the gene product and any agent that modulates Kupffer cell function in the subject, wherein the agent is administered less than 1 hour prior to administration of the viral vector. Claim 35 further limits the agent to being administered less than 5 minutes before administration of the viral vector.

Claim 36 is similar to claim 34, but limited to concurrent administration.

Claim 37 is similar to claim 34, but does not limit the administrations by method or time-frame, and requires the agent to be any particle sufficient for phagocytosis having a diameter of about 10 to about 1000nm.

Claims 47-49 encompass a method of modulating the toxicity associated with a virally encoded transgene, the method comprising administering to any subject, via any method and in any time frame, any virus encoding any transgene and any agent that modulates Kupffer cell levels or modulates any Kupffer cell function in the subject. Claims 48-49 require, alternatively, the administration of the agent before administration of the virus encoding the transgene or the toxicity being hepatotoxicity.

Claim 39 limits the viral vector of claims 34-38 to adenoviral vectors.

Claims 41-42 limit the subject of claims 1 and 34-38 to primates or humans.

Claims 44 and 46 limit the methods of administration or viral vectors of claims 34-37 to one of fifteen methods or replication defective viral vectors.

Claim 45 limits the methods of administration of claims 1 and 34-37 to one of fifteen methods.

The aspects considered broad are: the breadth of any agent that modulates Kupffer cell function, the breadth of any viral vector that modulates Kupffer cell function, any method of administration to affect any tissue, the increase of expression of any transgene in any tissue, transgene not operably linked to expression control elements (which will be further shown to be required to be for expression in liver cells due to the other limitations), the administration of agents that modulate Kupffer cell function subsequent to the administration of the virus encoding the transgene, increasing the expression in any tissue, particles that modulate Kupffer cell function outside the diameter of 70-100nm, and methods of modulating the toxicity of a virus-encoded transgene.

As will be shown below, these broad aspects are not enabled for their full scope embraced. And, due to such lack of enablement, some claims are not enabled whatsoever.

The Nature of the Invention

The invention is in the nature of increasing the levels of any virus-encoded transgene in any tissue of any subject via the administration of any agent that modulates Kupffer cell function. Additionally, the invention is in the nature of modulating the toxicity associated with any virally-encoded transgene in any tissue of any subject, comprising the administration of any agent that modulates Kupffer cell levels or Kupffer cell function. Such invention, because it does not require a therapeutic effect, is interpreted to have use in the art for treating humans: e.g., in clinical trials.

However, the Nature of such Invention is within the broad genera of gene therapy, and gene therapy is not generally enabling of Applicant's invention due to problems with, *inter alia*, targeting and expression of transgenes in any particular tissue. For purposes to be shown in the state of the prior art, (i.e., Kupffer cells only act in the liver and other cells filter out viral particles in other tissues), the question of targeting is discussed with respect to the only enabled tissue: that of the liver.

To wit, Ghosh, et al. (2000) J. Hepatol., 32(Suppl. 1): 238-52, evinces an optimistic outlook for the targeting of liver tissue with viral vectors (ABSTRACT), but also acknowledges that the art is not yet generally enabling for targeting liver tissue, with any vector, through any particular method of administration (e.g., pp. 246-47, col. 2, last paragraph, "... it is risky to predict the future in this explosively expanding area, ..."; p. 248, col. 2, paragraph 2). Specifically, Ghosh recognizes that non-lentiviral retroviruses have problems infecting non-dividing cells, of which the liver is generally comprised (p. 241, col. 1, paragraph 2); problems with safety of lentiviral vectors mean that such lentiviral vectors may be destroyed before any transgene expression could be increased (e.g., p. 243, col. 1, paragraph 2), levels of gene expression problems exist for AAV vectors, as well as size-of-transgene limitations (p. 243, col. 2, paragraph 2), SV40 vectors are only known to infect liver through injection into the portal vein (p. 244, col. 2, paragraph 3), and baculoviruses have not been shown to infect liver cells *in vivo* (p. 246, col. 1, paragraph 3). Moreover, Ghosh specifically recognizes that transduction efficiency, integration, and levels of expression, despite increasing sophistication in the art, do not amount to practical long-term gene therapy approaches (p. 248). On the other hand, it is also disclosed by Ghosh that adenovirus types 2 and 5 have emerged as the most efficient means of

transferring genes to the liver and may be useful for short-term transgene expression (p. 248, col. 2, paragraph 3-p. 248, col. 1, paragraph 1).

Hence, from the Nature of the Invention, the Artisan would not reasonably predict that any other vector could be used to target and express transgenes in the liver is the adenoviral vector. Such is due to problems with targeting and expression, e.g., Ghosh, p. 249, col. 2, paragraph 3, and even adenoviral vectors would only be expected to produce short-term expression, e.g., Id. Moreover, the Artisan would not reasonably predict that such adenoviral vectors could be administered by any method other than intravenous injection or direct administration, which is bought about by the lack of reasonable predictability with regard to targeting: i.e., if such adenovirus were administered, for example, to muscle tissue, it would be taken up by the muscle before it even reached the liver tissue (Ghosh, p. 244, last paragraph), as it transforms a wide variety of tissues. In addition, logic dictates that if liver cells are being transformed, the transgene must be operably linked to expression control elements for expression in liver cells, otherwise the transgene would not be expressed in the first place.

With regard to the administration of any viral nucleic acid encoding a transgene, no virally encoded transgene could be administered and have expression of such transgene. Such is because the nature of administration of any viral nucleic acid, except that of positive-strand RNA viruses would even express the transgene. This is because the virus nucleic acid requires the presence of proteins contained within the viral particle to effect viral expression and maintenance. For example, the retroviruses require a viral-particle-contained reverse transcriptase to make a copy of DNA from which the transgene could then be transcribed (e.g., Telesnitsky, et al. (1997) Retroviruses, Edited by Coffin, et al., Cold Spring Laboratory Press,

Plainview, NY., pp. 128-129). Hence, the Artisan could not reasonably predict that any particular viral nucleic acid could be used to transform any cell type and have expression of the transgene encoded.

The State of the Prior Art

The state of the prior art is effectively summarized by the references of Wolff, et al. (1997) J. Virol., 71(1): 624-29 and Tao, et al. (2001) Molec. Ther., 3(1): 28-35.

What the prior art demonstrates is that prior depletion of macrophages in the liver (the Kupffer cells) results in higher transformation of liver cells with subsequently administered adenoviral vectors, with delayed clearance and higher levels of gene expression in the liver (Wolff, ABSTRACT). It is noted that Wolff uses dichloro-MBP liposomes (p. 624, col. 1, last paragraph). Moreover, Wolff notes that these adenoviral vectors are intravenously administered (Id.). Hence, the Artisan could not reasonably predict that by acting on Kupffer cells, transformation of any other tissue than liver could occur, because the macrophages of those other tissues would be reasonably predicted to interfere with such transfection, further exacerbating the targeting problems in the nature of the invention. Therefore, the Artisan would not be able to reasonably predict transformation of any other tissue other than liver.

Applicant's article, Tao, et al. (2001) Molec. Ther., 3(1) : 28-35, demonstrates a different method of increasing transgene expression in a tissue by affecting Kupffer cells (TITLE). Specifically, Tao, describes a method similar to Wolff, but substituting a low dose of an adenoviral vector not encoding the transgene for the dichloro-MBP liposomes, which are also administered intravenously (ABSTRACT; FIGURE 2). To explain the effect of such administration, Tao argues that the Kupffer cells act as a biological filter, and they hypothesize

that such filtration is transiently saturated, allowing efficient delivery of the second administered adenoviral vector with the transgene. Further, Tao states that the effects are not seen when the adenovirus without transgene is administered after the adenovirus encoding the transgene (pp. 32-33, paragraph bridging pages). Lastly, Tao demonstrates that other compounds, e.g., doxorubicin, are known to deplete such Kupffer cells with the same effect (p. 32, col. 1, paragraph 2).

Hence, given that the Art had not yet determined the mechanism through which such adenoviral vectors actually modulate Kupffer cell function, the Artisan would not find it reasonably predictable that any viral vector or any compound that modulates any Kupffer cell function would allow any other viral vector encoding a transgene to show increased expression. Such is because the mechanisms of Kupffer cell "filtering" may differ for the different viruses, and because the Art does not even know that the "filtering" mechanism even exists. Also, given that a number of compounds, typically liposome-encapsulated compounds, are known in the art to deplete Kupffer cells, the Artisan would have been able to predict that any compound that depeletes Kupffer cells would work in Applicant's methods of increased expression, provided such compounds were administered prior to, or concurrently with, the transgene-encoding adenovirus.

Next, because such agents that modulate Kupffer cell function are limited to adenoviruses, the size of such particles is limited to that of adenovirus particles. Adenoviruses are limited in size to 70-100nm, as evidenced by Shenk (2001) Fundamental Virology, 4th Ed., Edited by Knipe, et al., by Lippincott, Williams, and Wilkins, New York, NY., p. 1054. Hence,

the Artisan would not be able to reasonably predict any other size of the particle to be any other than 70-100nm.

With regard to the claims of modulating the toxicity associated with a virally encoded transgene, Lieber (1997) J. Virol., 71(11): 8798-8807 is the closest prior art of record. Lieber demonstrates that while TNF elevations can be dampened by such administrations by administration of galladinium chloride, which also depletes Kupfer cells, Il-6 release was enhanced (p. 8805, col. 1). Moreover, such toxicity is not associated with the transgene, but with the virus itself (Id.). Further, any specific toxic transgene's toxicity would not be modulated. For Example, ricin effects translation, and as such, would still be toxic, no matter what effects the Kupffer cells may exert (Olsnes, et al. (2001) Toxicon 39: 1723-28). Hence, from Lieber, the Artisan would not be able to reasonably predict that toxicity would be reduced for any transgene, and because the toxicity is from the virus, the Artisan would not be able to reasonably predict that any toxicity would be reduced for any virus, because the compensating IL-6 release may more than make up for any particular beneficial effects from the loss of TNF expression.

Hence, from the nature of the invention and state of the art, the Artisan would not be able to reasonably predict that any tissue could be so-transformed, that any agent that modulates Kupffer cell function could be used, that any viral vectors could be used, that any transgene not operably linked to expression control elements for liver expression could be used, that the agent could be delivered after the administration of the adenovirus-encoded transgene, or that any size particle of virus could be used.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and the demonstrated lack of reasonable predictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation, for its fully claimed scope.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose the mechanism of action of the adenoviral vector on Kupffer cells, that Kupffer cells exist in other tissues, that any vector could transform liver through any method, that any virus can act on Kupffer cells as adenoviral vectors do, that any other agent can modulate Kupffer cells, that any viral nucleic acid can transform cells, that any expression control elements work in the liver, that adenoviral particles may be of any claimed size, the Artisan could not predict, in the absence of proof to the contrary, that such applications as Applicant claims would be efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount of Direction and Guidance Provided By Applicant

The specification broadly discloses that there is a need for better control of transgene expression in adenoviral vectors due to the problem of balancing the amount of adenovirus used against the levels of expression attained (pp. 1-2), that the invention is based in part on the discovery that the dose-response of adenoviral delivery and expression is non-linear, and that

depletion of Kupffer cells can also enhance expression levels (p. 2), further explaining that, not wishing to be bound by theory, the low dose of adenoviral vectors likely enter the Kupffer cells, thereby saturating the Kupffer cell's ability to uptake more adenovirus, and the second administration is more effective to infect other cells of the liver (pp. 2-3). Pages 2-7 broadly track claim language. Pages 8-22 broadly discuss various transgenes, methods of vector use, adenoviral vectors, lowering Kupffer cell levels by various compounds, pharmaceutical compositions, and many methods of administration.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any tissue may be transformed by acting on Kupffer cells, that any viral vector can effect Kupffer cells such that any other viral vector could be reasonably predicted to infect even non-Kupffer cells, even of the liver, that any methods of administration but direct administration and intravenous administration could infect liver tissues, that any viral vector could infect liver, that any viral nucleic acid could infect liver and produce transgene products, that any modulation of Kupffer cell function could cause increased infection and/or expression of any virally encoded transgene, that any transgene not operably linked to expression control elements of the liver would even be expressed, that any method of administration may be used to transform liver cells, that any agent affects Kupffer cell function besides adenovirus vectors, that toxicity of virally encoded transgene can be modulated in any reasonably predictable fashion, that agents may be administered after the adenoviral vector, or any vector for that matter, that any agent that modulates Kupffer cell activity could be other than 70-100nm in size, or that subsequent administration of the agent will produce effects.

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the information to provide reasonable predictability.

The Existence of Working Examples

Applicant's examples roughly track the information provided by the disclosure of Tao, et al. (2001) Molec. Ther., 3(1) : 28-35. Specifically, Example 1 demonstrates that co-administration of adenoviral vectors encoding a reporter with an adenoviral vector encoding IFN-beta causes increased levels of transformation of cells and subsequent expression, in the liver of mice, when such vectors are administered intravenously. Example 2 demonstrates that such dose responses are not due to an effect of the IFN-beta encoded in the adenovirus. Example 3 demonstrates that prior or concurrent administration of the adenovirus encoding the transgene is sufficient for increased IFN-beta expression. Example 4 demonstrates that modulation of the dose-response is dose-dependent, but the promoters are still promoters active in liver cells. Example 5 demonstrates that doxorubicin may be used to deplete the Kupffer cells, providing the same response as the adenovirus encoding the reporter gene, and such effects may be seen in 4 of 5 mouse types. Example 6 demonstrates similar effects in rhesus monkeys, but with a different dosage-inflection point.

However, such information is still not enough to reasonably predict that any tissue may be transformed by acting on Kupffer cells, that any viral vector can effect Kupffer cells such that any other viral vector could be reasonably predicted to infect any non-Kupffer cells, even of the liver, that any methods of administration but direct administration and intravenous administration could infect liver tissues, that any viral vector could infect liver, that any viral nucleic acid could

infect liver and produce transgene products, that any modulation of Kupffer cell function could cause increased infection and/or expression of any virally encoded transgene, that any transgene not operably linked to expression control elements that are functional in the liver would even be expressed, that any method of administration may be used to transform liver cells, that any agent affects Kupffer cell function besides adenovirus vectors, that toxicity of virally encoded transgene can be modulated in any fashion, that toxicity of virus could be modulated in any fashion, that the agent affecting Kupffer cells may be administered after the adenoviral vector, or any vector for that matter, that any agent that modulates Kupffer cell activity could be other than 70-100nm in size, or that subsequent administration of the agent will produce effects.

The Amount of Experimentation is Undue

Because the Artisan could not reasonable predict that any tissue may be transformed by acting on Kupffer cells, that any viral vector can effect Kupffer cells such that any other viral vector could be reasonably predicted to infect any non-Kupffer cells, even of the liver, that any methods of administration but direct administration and intravenous administration could infect liver tissues, that any viral vector could infect liver, that any viral nucleic acid could infect liver and produce transgene products, that any modulation of Kupffer cell function could cause increased infection and/or expression of any virally encoded transgene, that any transgene not operably linked to expression control elements that are functional in the liver would even be expressed, that any method of administration may be used to transform liver cells, that any agent affects Kupffer cell function besides adenovirus vectors, that toxicity of virally encoded transgene can be modulated in any fashion, that toxicity of virus could be modulated in any fashion, that the agent affecting Kupffer cells may be administered after the adenoviral vector, or

any vector for that matter, that any agent that modulates Kupffer cell activity could be other than 70-100nm in size, or that subsequent administration of the agent will produce effects, the Artisan would have to perform extensive experimentation with each of these parameters to find the working embodiments embraced by Applicant's claims, and as such, this experimentation would be considered undue, essentially amounting to inventing Applicant's claimed subject matter for themselves.

Conclusion

Because the Artisan would have had to perform an undue amount of experimentation to reasonably predict the working embodiments, Applicant's invention is not enabled for any methods of modulating toxicity, increasing transformation/expression of transgenes in any tissue, any viral vector except adenoviral vectors, any agent that modulates Kupffer cell activity, particles outside the range of 70-100nm, any viral nucleic acid, administration of agent after the administration of adenovirus encoding a transgene, the absence of operably linked expression control elements for liver cell expression, or any method of administration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 34-41, 43-46 and 52-53 rejected under 35 U.S.C. 102(a) as being anticipated by Tao, et al. (2001) Molecular Therapy, 3(1): 28-35.

For this rejection it is further noted that Gao discloses essentially the same subject matter of the instant Application, and further that Barsoum, Parr, and Fawell are the inventive entity of this Application; however, the Tao article states that Tao, Gao, Parr, and Fawell each contributed equally to the paper, leading the Examiner to believe that Tao, Gao, Parr, and Fawell must be inventors, and if Barsoum did not contribute equally, it would also appear that Johnston, Wilson, and Baradet should also be considered as the inventive entity of this Application. Applicant is requested to clarify these ambiguities in the response to this action.

With regard to claims 1, 36, 37, 38, 43, and 54, Gao discloses that co-administration of adenoviral vectors encoding alternatively lacZ and IFN-beta, leads to an enhancement of the expression of IFN-beta expression in mice (e.g., FIGURE 2). Moreover, such adenoviral vectors are replication defective (p. 29, first paragraph). Furthermore, such disclosure also discloses the pharmaceutical composition which comprised both vectors, as well as inherently comprising a pharmaceutically acceptable carrier: water (without water, the vector could not be injected), because the composition was mixed (FIGURE 2, legend).

With regard to claims 34-35, 39, 41, 44, 45, and 46, Gao discloses administration of a viral vector encoding a reporter gene at 1 hour or 5 minutes before administration of an adenoviral vector encoding IFN-beta, leading to increased liver expression of IFN-beta after intravenous administration. Moreover, such adenoviral vectors are replication defective (p. 29, col. 1, paragraph 2). Further, Gao discloses this same response curve for administrations to rhesus monkeys.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tao, et al. (2001) Molecular Therapy, 3(1): 28-35.

With regard to claims 34 and 41, Gao discloses administration of a viral vector encoding a reporter gene at 1 hour or 5 minutes before administration of an adenoviral vector encoding IFN-beta, leading to increased liver expression of IFN-beta after intravenous administration. Moreover, such adenoviral vectors are replication defective (p. 29, col. 1, paragraph 2). Further, Gao discloses this same response curve for administrations to rhesus monkeys. Moreover, the dose-response curves were similar in four of five mouse strains tested (p. 32, col. 2). Lastly, Gao suggests using these same methods in humans (p. 35, col. 1).

Therefore with regard to claim 42, at the time of invention by Applicant, it would have been obvious to use the methods of Gao in increasing the level of adenovirally-encoded transgene product in livers of humans. The Artisan would have been motivated to do so because dramatic increases in protein levels resulting from increases in viral dose can be obtained (p. 32, last paragraph). Moreover, the Artisan would have had a reasonable expectation of success, because similar methods worked in 4 of 5 mouse strains, as well rhesus monkeys, indicating broad inter-species applicability.

Note to Applicant

Applicant should note that claims 47-49 were not rejected as anticipated by Tao, et al. (2001) Molecular Therapy, 3(1): 28-35. Such is because Tao, while teaching the method steps and compositions, does not make it reasonably predictable that the toxicity of a virally encoded transgene could be modulated.

Also, Wolf, et al. (1997) J. Virol., pp. 624-29 teaches administration of compounds that deplete levels of kupffer cells thereby increasing subsequent transformation and expression of transgenes from adenoviral vectors in liver is the closest prior of art record to Applicant's claimed methods and compositions outside of those rejections provided.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert M. Kelly, Ph.D.
Examiner, USPTO, AU 1633
2C55 Remsen Building
(571) 272-0729

DAVE TRONG NGUYEN
PRIMARY EXAMINER
SPE 1633